# Single-use systems underline the rising significance of extractables and leachables studies

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Examining extractables and leachables is an important safety issue as these substances can adversely impact the health of patients. While assessing impurities arising from the synthesis and degradation of the pharmaceutical product itself has received much consideration over many years, greater attention is now being paid to the migration of mobile chemical substances from plastic components used in the packaging and manufacturing processes of pharmaceutical products.

Testing for leachables (substances that migrate under normal conditions) and extractables (those that migrate when exposed to solvent under harsh conditions) is critical for the pharmaceutical and medical device industries where packaging safety and toxicology studies are required for product registration. To enable the identification of potential extractables, the materials are exposed to stressing conditions such as strong solvents, elevated temperatures, and/or increased surface area. Substances observed are identified and characterized per appropriate FDA, USP, or ICH guidelines and further evaluated by a toxicologist to determine if the substance is a potential hazard.

## A new challenge: single-use systems

Single-use manufacturing systems, now widely used in the pharmaceutical industry, are for the most part made from plastic materials, and can be used to replace many of the fixed stainless steel components that previously predominated process equipment. The transition has facilitated a more flexible way of manufacturing pharmaceuticals and led to the current hot topic of continuous manufacturing. It allows rapid switching between different products in the same manufacturing suite, simply by exchanging one module for another once a run is complete.

However, single-use systems come with their own challenges, notably extractables and leachables. A safety assessment must be performed to ensure that the polymeric materials coming into contact with the drug product do not contain impurities that might migrate out of the material and into the final product at a level that negatively impacts patient safety. Leachable substances also have the potential to impede a drug's efficacy or cause production issues. For example, a breakdown product of the secondary antioxidant Irgafos 168, found in polyethylene-film based bags, has been discovered to inhibit cell growth.

## Regulatory Expectations for E&L Evaluation

Although formal guidelines for E&L assessments have not yet been enacted for Single Use Systems, there is nonetheless a regulatory expectation that researchers will test for these potentially harmful contaminants. Agencies such as the FDA's Center for Biologics Evaluation and Research recommend a risk-based approach to evaluation. As discussed, the purpose of evaluating extractables & leachables is to demonstrate patient safety with respect to the identity and quantity of potential leachables in the final drug product and their potential toxicity to patients. The purpose is not to test every material that comes in contact with the product during the manufacturing process, but to

evaluate the risk and perform extractables testing based on the risk assessment. The risk assessments published by both BPOG and USP <1665> draft, Characterization of Plastic Materials, Components, and Systems Used in the Manufacturing of Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products. evaluates criteria including temperature and duration of contact, chemical nature of the process stream, materials of construction, and distance to the final drug product/clearance steps.

## Single-use system testing

Over the last few years, the implementation of specific extractable protocols for single-use manufacturing systems have been based on two main efforts: the Biophorum Operations Group (BPOG) industry protocol and USP <665> for fluid-contact plastic components used in pharmaceutical processing, which is still in draft form and yet to be finalized. The USP <665> draft guidance does not define any requirements for analytical techniques, while the BPOG extractables protocol specifies the use of liquid (LC) and gas chromatography (GC) linked with mass spectrometry (MS) for identification and quantitation.

## Reference materials for extractables and leachables

Reference standards may be used for a variety of purposes, for example to calculate a relative retention time, ascertain system suitability, determine accuracy and identify impurities. It is preferable to use reference materials that are certified to quantify a specific extractable compound by a response factor or a calibration curve.

Given the number and chemical diversity of extractables, it is unreasonable to expect that authentic reference compounds will be available to confirm each and every identification. It is therefore necessary that levels of identification confidence be established and appropriately utilized. Data typically available from GC/MS and LC/MS analyses are used to identify individual extractables. Certified reference materials can streamline this identification process, especially for priority substances of toxicological concern. These materials are commercially available as individual compounds or as mixtures of a larger number of common extractables.